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Identification of genetic markers for productive life in commercial sows

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Abstract
Escalating replacement rates and production costs warrant attention on sow productive life (SPL). Increasing average SPL by one-tenth of 1 parity would result in an annual revenue increase of over $15 million in the United States. Research in model organisms has revealed conserved genes and gene pathways that lead to longer lifespan. The most prominent gene pathways are those involved in growth, most notably genes in the IGF pathway that serve to mimic the response of caloric restriction. The objective of this research was to test the hypothesis that these well conserved genes and gene pathways could also play a role in SPL, even though the productive life of sows is both a measure of longevity and their reproductive performance. Preliminary research on 3 distinct populations of over 2,000 animals suggested that several genes were associated with components of SPL. Genetic markers were then analyzed against the corresponding records of the sows for reproductive and longevity traits using a validation population of 2,000 commercial females. Right censored data were used to test associations of genetic markers with survival to defined time points. Three distinct models of survival analysis were implemented using nonparametric estimates of the survival distribution in a sequential order, using a parametric accelerated failure time model with a Weibull distribution of the error term, and a Cox proportional hazards model, which is a semiparametric model that uses an unspecified baseline hazard function. The genetic markers *CCR7* and *CPT1A* were significantly associated ($P < 0.05$) with survival using the nonparametric model and tended ($P < 0.1$) toward significance using the parametric and semiparametric models with significantly different effects ($P < 0.05$) between some genotype classes. Genetic markers for *MBL2*, *IGFBP3*, and *WARS2* also tended ($P < 0.1$) toward significance for survival traits, but were not consistent. Mixed model analyses were used to determine the associations of these genetic markers with reproductive traits. The genetic markers for *IGFBP1*, *MBL2*, *CPT1A*, *CCR7*, *SLC22A5*, and *ACE* were significantly ($P < 0.05$) associated with at least 1 reproductive trait. These results show that molecular markers should be considered for use in marker-assisted selection to improve SPL.

Keywords
longevity, pig, reproduction, sow productive life

Comments
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Identification of genetic markers for productive life in commercial sows[1]

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ABSTRACT: Escalating replacement rates and production costs warrant attention on sow productive life (SPL). Increasing average SPL by one-tenth of 1 parity would result in an annual revenue increase of over $15 million in the United States. Research in model organisms has revealed conserved genes and gene pathways that lead to longer lifespan. The most prominent gene pathways are those involved in growth, most notably genes in the IGF pathway that serve to mimic the response of caloric restriction. The objective of this research was to test the hypothesis that these well conserved genes and gene pathways could also play a role in SPL, even though the productive life of sows is both a measure of longevity and their reproductive performance. Preliminary research on 3 distinct populations of over 2,000 animals suggested that several genes were associated with components of SPL. Genetic markers were then analyzed against the corresponding records of the sows for reproductive and longevity traits using a validation population of 2,000 commercial females. Right censored data were used to test associations of genetic markers with survival to defined time points. Three distinct models of survival analysis were implemented using nonparametric estimates of the survival distribution in a sequential order, using a parametric accelerated failure time model with a Weibull distribution of the error term, and a Cox proportional hazards model, which is a semiparametric model that uses an unspecified baseline hazard function. The genetic markers *CCR7* and *CPT1A* were significantly associated ($P < 0.05$) with survival using the nonparametric model and tended ($P < 0.1$) toward significance using the parametric and semiparametric models with significantly different effects ($P < 0.05$) between some genotype classes. Genetic markers for *MBL2*, *IGFBP3*, and *WARS2* also tended ($P < 0.1$) toward significance for survival traits, but were not consistent. Mixed model analyses were used to determine the associations of these genetic markers with reproductive traits. The genetic markers for *IGFBP1*, *MBL2*, *CPT1A*, *CCR7*, *SLC22A5*, and *ACE* were significantly ($P < 0.05$) associated with at least 1 reproductive trait. These results show that molecular markers should be considered for use in marker-assisted selection to improve SPL.

Key words: longevity, pig, reproduction, sow productive life

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INTRODUCTION

Sow longevity or sow productive life (**SPL**) has become a discussion point in the US commercial swine industry. Unacceptable replacement rates occurring on commercial farms are being driven by increased culling and mortality levels. Increased culling and mortality levels suggest that many breeding females do not produce a third litter, the point when most females recover their investment costs (Stalder et al., 2000, 2003). Recent analysis of the commercial sow herd shows that 42% of the females that enter the farm wean 30 or fewer pigs before they are culled and 94% are culled before they wean 57 pigs (Anil and Deen, 2007). Current replacement rates place the burden of being profitable on a relatively small percentage of sows that remain productive beyond the average sow (Stalder et al., 2000, 2003; Pla et al., 2003). Additionally, having a high replacement rate leads to having a greater than ideal proportion of parity 1 females in the herd, whose offspring are typically slower growing and endure more

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health-related problems compared with offspring from older sows (Moore, 2001).

Researchers working with model organisms such as mice, nematode, yeast, and the fruit fly have identified genes and gene pathways that are conserved between the species that lead to longer lifespan of these organisms (Hasty et al., 2003; Hekimi and Guarente, 2003; Longo and Finch, 2003; Simon et al., 2003; Tatar et al., 2003). The objective of this research was to test the hypothesis that these well conserved genes and gene pathways could also play a role in SPL, even though the productive life of sows is a measure of longevity and their reproductive performance during that time frame. Therefore, genes involved in the IGF pathway, along with genes more specific to reproductive traits, were targeted for marker development and association analyses in the evaluation of length of productive life among commercial breeding females.

MATERIALS AND METHODS

This research was approved by Iowa State University Animal Care and Use Committee.

Animal Population and DNA Isolation

Three populations (n = 2,300) of Large White and Landrace influenced lines consisting of pigs derived from mid-1990s genetics were initially used to test the associations and informative value of the identified genetic markers with the number of litters that sows produced or the number of pigs that sows produced in early parities. These populations were useful to screen genetic markers, but a more current data set with both reproduction and culling reasons was needed to identify markers that are associated with sow productive life.

A population used to validate previous association results was isolated and consisted of a total of 2,000 breeding age females, representing the most current genetic females available. All analysis presented herein is from this validation population. These females were from a large Midwestern commercial swine operation with 120,000 breeding females in their system. Five hundred females from each of 2 farms (farm 1 and farm 2) that both possessed 3,200 females in production were selected, and an additional 1,000 females were selected from a third farm (farm 3) that had 5,000 sows in production. The 11,400 sows from the 3 herds in the study represent 9.5% of the 120,000 breeding females in production in this commercial system. The females from farms 1 and 2 were line 42 females (Large White $\times$ Landrace F_1), whereas the females from farm 3 were from the Camborough 22 line (Large White, Landrace, and Duroc composite). Both lines analyzed are commercially available lines produced by Pig Improvement Company (PIC, Hendersonville, TN). Equal numbers of parity 0 females (replacement gilts) and females that had produced a minimum of 5 litters were selected from each farm. The parity 0 females ranged in age from approximately 7 mo to those that were about to farrow and are hereafter termed young females. The females with a minimum of 5 parities ranged from parity 5 to parity 13 and are hereafter termed parity 5+ females. Other than the criteria for age group, the females were randomly selected with all young females being classified as acceptable replacement females by the management and workers from each of the 3 participating farms. The parity 5+ females were selected as a means of acquiring a greater volume of culling information from older sows in a more timely manner compared with the time required to identify a group of selected replacement gilts to attain the advanced parities or age examined in this study. Ear tissue was isolated on the 2,000 commercial females described above using the TypiFix ear tag from IDnostics (Schlieren, Switzerland). This system allows for simultaneous identification and tissue collection to prevent sample misidentification. The DNA was then isolated from the tissue samples using the Nexttec DNA isolation system (Leverkusen, Germany), adhering to the manufacturer's protocol. More information on this population in terms of reproductive rates, removal reasons, and age was reported by Mote et al. (2009).

Genetic Markers

Single nucleotide polymorphisms were identified in 20 genes (*IGFBP1*, *IGFBP2*, *IGFBP3*, *IGFBP5*, *IGFBP7* (Oh et al., 1996), *carnitine O-palmitoyltransferase I* (***CPT1A***), *organic cation/carnitine transporter* 2 (*solute carrier family 22 member 5*; ***SLC22A5***), *angiotensin I converting enzyme* (***ACE***), and *C-C chemokine receptor 7* (***CCR7***), *tryptophanyl tRNA synthetase 2* (*mitochondrial*; ***WARS2***), *tryptophanyl tRNA synthetase* (*cytoplasmic*; ***WARS***), *cyclooxygenase 2* (***COX2***), *tryptophan/serine protease* (***UNQ9391***), *vitamin D receptor* (***VDR***), *calmodulin* (***CALM1***), *superoxide dismutase 1* (***SOD1***), *mannose-binding lectin 2* (***MBL2***), *copper chaperone for superoxide dismutase* (***CCS***), *IGF2 receptor* (***IGF2R***), and *β 2 adrenergic receptor* (***B2AR***) that could be classified into one or more of the following groups: insulin/growth, reproduction, nutrition, health, anti-inflammatory, or longevity. Classification of genes was based on current reported physiological roles for the genes. All genetic markers that were tested for this project are listed in Tables 1, 2, and Supplemental Table A (http://jas.fass.org/content/vol87/issue7/).

Data Collection

PigCHAMP production records were obtained throughout the research trial (20 mo) by downloading the database of the farm with the farm identification number of the sow and correlating it to the TypiFix ear tag. The data that were collected regarding the productive life of the sows included the date the sow entered the herd, first service date, removal date, removal parity, removal type (cull, mortality, or killed), removal

Table 1. Genetic markers associated with at least 1 component of sow productive life in this population and their related SNP information from a study of candidate genes on sow productive life

Gene[1]	Forward/reverse primer (5′–3′)	PCR size	Location[2]	SNP[3]: position[4]	Enzyme	Allele 1	Allele 2	Allele 1 frequency, %
ACE	TCATCATCCAGTTCCAGTTCC/ GTTCGGCGTCCAGTTGTACT	540	Intron 12	C/T: 95	AluI	369, 102, 36, 33	276, 102, 93, 36, 33	33
CCR7	AAGTCCTGGGTCTTCGGAGT/ GGATGATGACGAGGTAGCAGA	385	Exon 3	C/T: 147	HpyCH4III	385	240, 145	59
CPT1A	AGCTCTAGTTGGTTGTGGAATC/ ACCTACGGGTAAGCGGGAAC	350	Intron 11	T/C: 87	BstNI	299, 51	212, 87, 51	69
IGFBP1	AAAATCAGGGTATCGGTCTTCA/ TCGTTCCTGTGCCATCTACA	403/393	Intron 2	CATCCCCAGG[5]: 252	BtsCI	302, 91	160, 125, 91, 26	58
IGFBP3	CAAGTCTCAAGCACGGACAC/ GCCAGGGGCTCTCTCTTTT	438	Intron 2	A/G: 114	BsaHI	438	326, 112	62
MBL2	ACCTGCCTTGTGATTTCCTG/ GAATGCCAGAGAGTCAGAGC	251	Exon 1	T/C: 63	Bsp1286I	251	189, 62	42
SLC22A5	CCTGCCCTACATTCTCATGG/ CACTCTGGGGCTTTCTTCAC	539	Intron 9	C/G: 235	HaeIII	374, 165	304, 165, 70	33
VDR	ACCAGATCGTGCTGCTGAAG/ GGGAGACGATGCAGATGG	404	Intron 8	T/C: 220	HpyCH4IV	279, 125	185, 125, 94	21
WARS2	CAATTACCTGGGAGCCATTG/ CTTCTCTGGGTTTATGCCACA	175	Exon 2	G/A: 214	PstI	175	142, 33	79

[1]*ACE = angiotensin I converting enzyme*; *CCR7 = C-C chemokine receptor 7*; *CPT1A = carnitine O-palmitoyltransferase I*; *MBL2 = mannose-binding lectin 2*; *SLC22A5 = organic cation/carnitine transporter* 2 (*solute carrier family 22 member 5*); *VDR = vitamin D receptor*; *WARS2 = tryptophanyl tRNA synthetase 2* (*mitochondrial*).

[2]The position of the SNP within the gene.

[3]The first base by convention is allele 1, and the second SNP is allele 2.

[4]The position of the SNP from the beginning of the PCR fragment.

[5]The CATCCCCAGG is a 10-bp insertion/deletion.

reason, lifetime nonproductive days, and total days in the herd. The reproductive data collected included farrowing date, gestation length, total born, number born alive, stillborn, mummies, total pigs weaned, lactation length, and wean-to-first-service interval for each parity that the sow produced. Means, maximum data points, and minimum data points were obtained using the Univariate procedure (SAS Inst. Inc., Cary, NC). The maximum and minimum data points were identified as possible outliers, and data were subsequently verified to ensure that they were within realistic bounds for a given trait.

Statistical Analysis

Sow productive life involves not only if an animal can survive, but also incorporates human intervention for culling decisions such as if a female is productive enough to remain in the herd, on top of the skill of the technician when inseminating the female. Because it is a complex trait, several types of data analysis were used to determine if the genetic markers were associated with different survival aspects of SPL. A Fisher's exact test, using the FREQ procedure in SAS, was initially used to determine if there was a significant difference between the genotypic frequencies of the sows that had produced at least 5 parities at the onset of the research project (parity 5+) and the gilts that had just entered the sows farm (young) that serves to represent the typical unselected females in a commercial herd. A Fisher's exact test was also employed to determine if there was a significant difference in the genotypic frequencies of the young sows that dropped out of production before they produced a fourth parity and those young sows that produced at least 4 parities. Survival analysis was also performed on the young sow group using 3 different methods. A nonparametric estimate of the survival distribution computed in a sequential order using PROC LIFETEST of SAS simultaneously computed a Log-Rank statistic that places more weight on differences between groups that occur at later points in time and a Wilcoxon statistic that gives more emphasis to differences between groups that occur at earlier time points. The LIFETEST procedure is useful for screening large numbers of quantitative variables, but it is not adequate for testing the effects of variables controlling other covariates. The LIFEREG and PHREG procedures in SAS can be used (Allison, 1995) to simultaneously account for the fixed effects of genotype of the sow and the farm on which she was housed. A parametric accelerated failure time model that uses a Weibull distribution for the baseline hazard function was fitted to the right censored survival time data using the PROC LIFEREG procedure of SAS. Sows that were still in the breeding herd the last time the populations were inspected are considered right censored because their failure times (dates when they are removed from the breeding herd) would occur at some time point after the herd was last inspected. A Cox proportional

Table 2. Genetic markers that were not associated with at least 1 component of sow productive life in this population and their related SNP information from a study of candidate genes on sow productive life

Gene[1]	Forward/reverse primer (5'-3')	PCR size	Location[2]	SNP[3]: Position[4]	Enzyme	Allele 1	Allele 2	Allele 1 frequency, %
COX2	TCAATCGACCAGAGCAGAGA/ CGAGCTGTGGATCTTGAACA	555	Intron 9	A/G: 172	BsrBI	555	386, 169	25
IGFBP2	GGAACTTGCTCACCCTTGTC/ CAGGAAGAAGCCCAGGTATG	361	Intron 2	A/T: 135	MboII	346, 15	200, 146, 15	68
IGFBP5	CGCCTGAGATGAGACAGGA/ GGACAGGAGGGGGTGAGAGG	312	Intron 2	C/A: 107	AvaI	252, 60	147, 105, 60	18
UNQ9391	TGTAGGGTCGCGTATGGACT/ GGGGTTGGTGGAGTGAGTAA	552	Intron 3	T/G: 194	BsmAI	504, 48	336, 138, 48	78
WARS	CCCTTGTTCCTGGTGTCACT/ GGCCACCACCACTGATTAAC	363	Intron 5	C/T: 214	MseI	345, 18	213, 132, 18	83

[1]*COX2 = cyclooxygenase 2; UNQ9391 = tryptophan/serine protease; WARS = tryptophanyl tRNA synthetase.*
[2]The position of the SNP within the gene.
[3]The first base by convention is allele 1, and the second SNP is allele 2.
[4]The position of the SNP from the beginning of the PCR fragment.

hazards model, which is a semiparametric model that uses an unspecified baseline hazard function, was also tested using the PROC PHREG procedure of SAS. The effects of farms were found to have a significant effect ($P < 0.02$) on survival. The line of the sows was also tested, but found not to be significant and, therefore, was not included in the final analysis. The fixed effects that were included in the final models for the LIFEREG and PHREG procedures were genotype of the sow and the farm on which the sows were housed. The LIFETEST analysis included only the genotype effects unadjusted for the effects of farms. For the 3 survival analysis tests, survival to parity 1, parity 2, parity 3, parity 4, 250 d post first service, 300 d post first service, and 500 d post service were tested to determine if a significant genotypic effect on survival existed. Data were right censored at the aforementioned time points for each sow that survived beyond said time point.

When the Weibull model is used for the baseline hazard functions, the accelerated failure time model used by LIFEREG is also a special case of the proportional hazards models used by PHREG. For both models, the hazard function for the *i*th genotype on the *j*th farm can be expressed as

$$h_{ij}(t) = h_o(t)\ \mathrm{e}^{\mu} e^{\alpha_i} e^{\beta_j}.$$

The hazard function at time t is the conditional probability that an animal will fail to survive the next time interval of some small length Δ given that the animal has survived up to time t, divided by the length of the interval Δ. Here, $h_o(t)$ is the baseline hazard function corresponding to the third farm ($\beta_3 = 0$) and the 22 genotype ($\alpha_3 = 0$). The LIFEREG analyses used a Weibull distribution to model the baseline hazard function, whereas the PHREG analysis does not specify any particular model for the baseline hazard function. For a specific farm, the ratio of the hazard functions for a specific genotype relative to the baseline genotype,

$$\text{relative risk} = \frac{h_{ij}(t)}{h_{3j}(t)} = \frac{h_o(t)\ \mathrm{e}^{\mu} e^{\alpha_i} e^{\beta_j}}{h_o(t)\ \mathrm{e}^{\mu} e^{\alpha_3} e^{\beta_j}} = e^{\alpha_i}$$

gives the relative risk of not surviving the next small time interval for the 2 genotypes. Because the Weibull model used in the LIFEREG analysis fit the data quite well, the LIFEREG and PHREG analyses produced similar results. The GLM procedure of SAS was used to determine genotype effects on the reproductive traits that were analyzed. The statistical model included genotype, farm, and age group (when the trait was analyzed using both the parity 5+ and young sow groups). The parity 5+ and the young groups were analyzed individually, as well as in a combined analysis of the 2 groups. The reproductive traits that were focused on were the total number of pigs born and the number of pigs born alive for each litter, as well as lifetime records for both traits. The sire and dam information for these sows was unknown, as is the usual case in commercial herds using pooled semen from several sires, and therefore, neither sire nor dam could be included as random effects. The genetic markers were tested for significant associations within each parity, as well as for combined lifetime productivity.

RESULTS

Initial analysis (data not shown) of the first 3 distinct populations totaling 2,300 breeding animals showed that 14 of the 20 genetic markers were associated with components of SPL (either survival to parity 6 or for reproductive traits), had informative allele frequencies, and thus warranted further research (Mote et al., 2006). The markers showing no tendency for association with any trait included in SPL were dropped from further analysis (see Supplemental Table A; http://jas.fass.org/content/vol87/issue7/). A fourth commercial population was identified to serve as our validation population that contained longevity and reproduction information.

Initial analysis of the validation population using Fisher's exact test demonstrated significant differences ($P < 0.05$) in the genotypic frequencies indicative that the marker could be involved in the ability of the sow to survive to parity 5. Seven of the remaining 14 genes showed a significant difference ($P < 0.05$) between the genotypic frequencies of the superior sows and the young gilts. These 7 genes were *IGFBP1*, *IGFBP3*, *CPT1A*, *SLC22A5ACE*, *CCR7*, and *WARS2*. Finding one-half of the genes tested in this population showing a significant difference is greater than chance alone and could be explained in part by the prescreening process. A correction for independently testing multiple markers was not conducted as more stringent tests for survival were conducted.

At the conclusion of the 20-mo trial when all of the young sows had had the opportunity to farrow 4 litters, data were again obtained from PigCHAMP software and were considered to be the final data set. The records from only the young sow group were then analyzed using a Fisher's exact test with the 14 genetic markers listed in Tables 1 and 2 to determine if a significant difference in genotypic frequencies existed between the young sows that were able to produce 4 parities and those that did not. The only genetic marker that showed a significant difference ($P < 0.05$) between the genotypic frequencies of the young sows that produced 4 litters and those that did not was *CPT1A* ($P < 0.05$), though *MBL2* tended ($P < 0.1$) toward significance.

The LIFETEST procedure of SAS was used to analyze the markers listed in Tables 1 and 2 to determine if there was a statistical difference in survival between the genotype classes of the young females, without adjusting for farm effects. When the LIFETEST procedure of SAS was used for data analyses on the young females, *CCR7* showed a significant association ($P <$

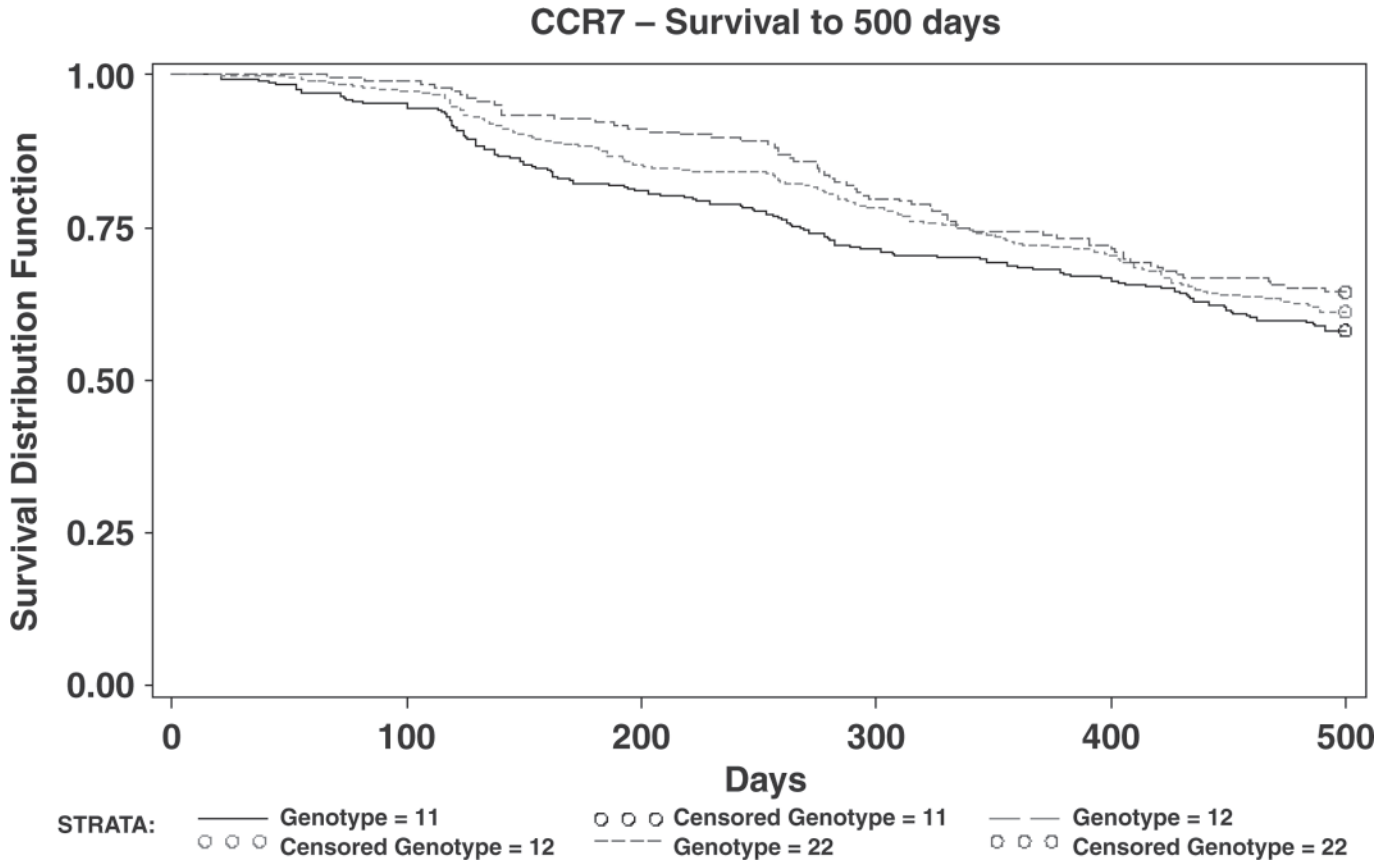

Figure 1. Survival curves for the 3 genotypes of C-C chemokine receptor 7 (CCR7) for sows up to 500 d in the herd. A significant difference was seen between the genotype classes at 250 and 300 d, but was not significant at later dates.

0.05) with survival to 250 d after first service, 300 d after first service, and survival to parity 1. A graph of the survival curve for *CCR7* can be seen in Figure 1. The marker for *CPT1A* showed a trend toward significance ($P < 0.1$) when all genotypes were included in the analysis of survival to parity 4. The fact that only 10% of the animals possessed the 22 genotype was a limiting factor inhibiting the 22 genotype from being significantly different from the other genotype classes. Additional genetic markers showing a tendency for association ($P < 0.1$) were *IGFBP3* with survival to 250 d after first insemination, *MBL2* with survival to parity 4, and *WARS2* with survival to 250 d after first insemination. Data analysis using the PHREG and LIFEREG procedures was performed on the genetic markers listed in Tables 1 and 2 and revealed the same outcome for the association tests of *CCR7* and *CPT1A*. The *CCR7* genetic marker showed a tendency ($P < 0.1$) for association with survival to 250 d after first service. The *CPT1A* gene once again showed a trend toward association ($P < 0.1$) with survival to parity 4. A compilation of all of the genetic markers that were significantly associated with sow survival is shown in Table 3. Though the genotype effects were shown to be significant at the $P < 0.1$ level, the difference between the 11 and 22 genotypes in each of these cases was significant at the 0.05 level, and the relative risk of the 11 genotype was significantly greater than that of the 22 genotype. The effect of the 12 genotype was only about 505 as large as the effect of the 11 genotype and was not quite significant at the $P = 0.05$ level. Estimates of relative risk and corresponding 95% confidence intervals are presented in Table 4.

The reproduction analyses of the genes listed in Tables 1 and 2 also proved to be beneficial to understanding the different roles these genes play in SPL. The genetic marker for *IGFBP1* was significantly associated with several reproductive traits for the different sow groups. The marker was significantly associated with the number of pigs born alive in parity 1 in the young sows with the favored genotype (22) having 1.2 and 1.0 more pigs born alive than the 11 and 12 genotypes, respectively. In the parity 5+ group, 12 and 22 genotypes were significantly different from the 11 genotype for the number of pigs born and the number of pigs born alive. In the parity 5+ group, the sows with the 12 or 22 genotypes had an advantage of at least 2.4 pigs born over the lifetime of the sow compared with the sows that possessed the 11 genotype. After dropping the 11 genotype class from further analysis (which represented less than 10% of the data), *MBL2* was significantly associated with early reproductive traits. It was significantly associated with the total number of pigs born and with the number of pigs born alive in parities 1 and 2 when all sows were analyzed together with the beneficial genotype class having an additional 0.35 pigs per litter for

Table 3. Association results of genetic markers with survival in sows in a study of candidate genes for sow productive life

Gene[1]	Trait	Fisher's exact[2]	PROC LIFETEST[3]	PROC LIFEREG[4]	PROC PHREG[5]
CCR7	250 d	$P < 0.05$	$P < 0.01$	$P < 0.07$	$P < 0.06$
CCR7	300 d	NS[6]	$P < 0.03$	NS	NS
CCR7	Parity 1	NS	$P < 0.04$	NS	NS
CPT1A	Parity 4	$P < 0.04$	$P < 0.1$	$P < 0.06$	$P < 0.06$
IGFBP3	250 d	NS	$P < 0.1$	NS	NS
MBL2	Parity 4	$P < 0.1$	$P < 0.06$	$P < 0.1$	NS
WARS2	250 d	NS	$P < 0.1$	NS	NS

[1]*CCR7 = C-C chemokine receptor 7*; *CPT1A = carnitine O-palmitoyltransferase I*; *MBL2 = mannose-binding lectin 2*; *WARS2 = tryptophanyl tRNA synthetase 2* (*mitochondrial*).

[2]Fisher's exact test between the genotypic frequencies of the young sows that survived to defined time point and those that did not.

[3]The LIFETEST procedure computes nonparametric estimates of the survival distribution in a sequential order.

[4]The LIFEREG procedure used fits a parametric accelerated failure time model with right censored data with a Weibull distribution of the error term.

[5]The PHREG procedure used fits a Cox proportional hazards model, a semiparametric model that uses an unspecified baseline hazard function.

[6]NS = not significant ($P > 0.10$).

all traits. Furthermore, *CPT1A* was significantly associated with reproductive traits as well, especially in the later parities. The favored genotype class (22) was associated with at least a 0.4 advantage in total number of pigs born and number of pigs born alive for all sows in parities 3 and 4. Additionally, the same genotype class had an advantage of 1.18 more pigs per year per sow for the young sows and had an advantage of 0.7 more pigs per year per sow for all sows combined. The genetic marker for *VDR* was significantly associated with total born in the young sows in parity 1 and with the lifetime number of pigs born alive in the young group of sows as well. Other markers such as SLC22A5, ACE, and CCR7 also were associated with some reproductive traits, though their effects were not as consistent across sow groups or parities. Complete results of all genetic markers that were significantly associated with reproductive traits are shown in Table 5.

DISCUSSION

In model organisms, the alleles associated with leaner phenotypes or associated with reduced caloric intake are often the preferred allele for longevity (Tatar et al., 2003). It has been shown that gilts that are leaner have the tendency to be removed from the herd sooner (Stalder et al., 2005). Furthermore, in swine production, one of the most critical points for sow survival is maximized feed intake during lactation. Sows that do not meet energy requirements during lactation often are in an energy deficit situation for several days during a typical 21-d lactation period and are subsequently in poorer body condition at weaning, which further contributes to increased wean to estrus intervals and culling from the breeding herd. Though for model organisms, reduced caloric intake is preferred for longevity and sows need to maximize feed intake during lactation, these same genes that are important for longevity in model organisms could still prove beneficial to SPL.

Several different methods to analyze sow survival for SPL were presented herein. The challenge with using the Fisher's exact test between the parity 5+ group and the young group was that it did not account for a founder effect or initial environmental conditions. Additionally, the beneficial genotype suggested using this method for CCR7 was the 11 genotype, which was the worst of the 3 genotypes when using any of the survival analysis methods. However, using a Fisher's exact test when analyzing just the sows in the young group that produced 4 parities or failed to produce 4 parities produced very similar results to the survival analy-

Table 4. Estimates of relative risk associated with genetic markers in sows in a study of candidate genes for sow productive life

		Marker 11 vs. 22		Marker 12 vs. 22		Marker 11 vs. 12	
Gene[1]	Trait	Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval
CCR7	250 d	1.91	(1.10, 3.32)	1.49	(0.90, 2.46)	1.28	(0.88, 1.86)
CPT1A	Parity 4	1.24	(0.82, 1.87)	0.97	(0.64, 1.46)	1.28	(1.04, 1.57)
MBL2	Parity 4	1.09	(0.78, 1.54)	1.19	(0.95, 1.48)	0.92	(0.68, 1.25)

[1]*CCR7 = C-C chemokine receptor 7*; *CPT1A = carnitine O-palmitoyltransferase I*; *MBL2 = mannose-binding lectin 2*.

Table 5. Genetic markers that were significantly associated with reproductive traits and the corresponding least squares means of the genotypes from a study on candidate genes for sow productive life

Gene[1]	Group	Trait	Parity	Pr > F	11 genotype	12 genotype	22 genotype
ACE	All sows	Born alive	Lifetime	0.01	61.92 ± 0.76	63.11 ± 0.38	64.77 ± 0.44
CCR7	Parity 5+	Born alive	4	0.05	12.46 ± 0.15	12.11 ± 0.16	11.34 ± 0.48
CPT1A	Young	Pig per day	Lifetime	0.05	0.068 ± 0.001	0.071 ± 0.001	0.073 ± 0.002
CPT1A	All sows	Total born	3	0.03	13.01 ± 0.14	13.47 ± 0.13	13.67 ± 0.31
CPT1A	Parity 5+	Total born	3	0.03	13.17 ± 0.18	13.30 ± 0.14	14.05 ± 0.28
CPT1A	All sows	Born alive	4	0.04	11.75 ± 0.14	12.25 ± 0.13	12.21 ± 0.30
CPT1A	Parity 5+	Born alive	4	0.01	11.87 ± 0.17	12.52 ± 0.13	12.31 ± 0.27
CPT1A	All sows	Total born	4	0.03	13.02 ± 0.15	13.58 ± 0.13	13.48 ± 0.32
CPT1A	Parity 5+	Total born	4	0.02	13.10 ± 0.17	13.71 ± 0.14	13.78 ± 0.28
IGFBP1	Young	Born alive	1	0.04	10.64 ± 0.20	10.90 ± 0.19	11.86 ± 0.42
IGFBP1	Parity 5+	Born alive	2	0.04	11.24 ± 0.19	11.88 ± 0.16	11.80 ± 0.27
IGFBP1	Parity 5+	Total born	2	0.02	12.05 ± 0.20	12.79 ± 0.16	12.61 ± 0.28
IGFBP1	All sows	Total born	4	0.02	13.05 ± 0.16	13.64 ± 0.14	13.04 ± 0.27
IGFBP1	Young	Total born	4	0.05	12.98 ± 0.30	13.70 ± 0.28	12.19 ± 0.63
IGFBP1	Parity 5+	Born alive	Lifetime	0.04	86.69 ± 0.78	89.09 ± 0.64	89.17 ± 1.12
MBL2	All sows	Total born	1	0.03	11.86 ± 0.24	12.24 ± 0.10	12.58 ± 0.14
SLC22A5	All sows	Born alive	4	0.04	12.15 ± 0.36	11.73 ± 0.13	12.19 ± 0.12
SLC22A5	Young	Born alive	4	0.04	12.55 ± 0.94	11.34 ± 0.26	12.18 ± 0.22
SLC22A5	All sows	Total born	4	0.03	13.28 ± 0.37	13.06 ± 0.14	13.59 ± 0.13
VDR	Young	Total born	2	0.04	NA[2]	13.00 ± 0.26	12.36 ± 0.16
VDR	Young	Born alive	Lifetime	0.05	NA	37.55 ± 0.52	36.34 ± 0.31

[1]*ACE = angiotensin I converting enzyme*; *CCR7 = C-C chemokine receptor 7*; *CPT1A = carnitine O-palmitoyltransferase I*; *MBL2 = mannose-binding lectin 2*; *SLC22A5 = organic cation/carnitine transporter* 2 (*solute carrier family 22 member 5*); *VDR = vitamin D receptor.*
[2]NA = not applicable.

sis results from the LIFEREG and PHREG analyses. Therefore, longevity analysis of an older group with a younger group should be avoided or could be an artifact of the Fisher test itself.

Sow productive life is a complicated trait to analyze because it is a combination of several different traits, all of which have a relatively large environmental component. Reproductive traits are notoriously lowly heritable (Roehe and Kennedy, 1995; Holl and Robison, 2003) with a low repeatability, though some managers still cull sows for poor reproductive performance based on a single record. Additionally, there is a lot of room for human error in the culling process itself; the culling reason listed for many sows can be inaccurate, and the culling reasons listed by farmers did not always match postmortem veterinarian analysis (Knauer et al., 2007). This leads to SPL having a low heritability (Serenius and Stalder, 2004). Therefore, it is not surprising that we did not find large effects, especially for the survival to later parities component of SPL.

The genetic markers for *CCR7* and *CPT1A* show the greatest promise for use as genetic markers for sow survival. The marker for *CCR7* was associated with early survival points, such as survival to 250 d after first insemination, 300 d after first insemination, and survival to parity 1. Survival to parity 1 is often overlooked, but should be the first critical time point that producers use as a benchmark to identify if they have problems with sow survival. Additionally, the consistency demonstrated by *CPT1A*, regardless of the type of analysis performed, leaves little doubt that it is associated with survival to parity 4. Survival to parity 4 is also a critical time point as sows typically need to produce at least 3 parities to recover their investment costs (Stalder et al., 2000, 2003). Sows that have the 12 genotype for *CPT1A* have a reduced hazard rate than the 11 genotype class when analyzed at survival to parity 4. If we were to extrapolate the data to estimate the mean survival times for the significantly different genotype classes, the mean survival of the 11 genotype class would be 4.58 parities and the mean survival for the 12 genotype would be 6.61 parities. This large effect is most likely overinflated because roughly one-half of the sows were still in production at the conclusion of the study and also does not account for producers who start to cull some sows at parity 6 for old age. However, it still stands that the sows with 12 and 22 genotypes have a greater chance of being profitable for the operation compared with animals having the 11 genotype. Both *IGFBP1* and *CPT1A* showed the clearest and most consistent associations with both the total number of pigs born and, more importantly, the number of pigs born alive. For *CPT1A*, the beneficial allele for reproductive traits is also the preferred allele for sow survival.

In summary, several markers were significantly associated with the sow survival portion or the reproductive portion of SPL. The *CCR7* gene should be considered in marker-assisted selection schemes for improved sow survival, and *IGFBP1* should be considered if selection pressure is warranted on reproductive traits. The inclusion of *CPT1A* in a marker-assisted selection scheme should improve both the sow survival and reproductive components of SPL and should therefore be strongly considered for improvement of sow productive life in commercial females.

LITERATURE CITED

Allison, P. D. 1995. Survival Analysis Using SAS: A Practical Guide. SAS Inst. Inc., Cary, NC.

Anil, S. S., and J. Deen. 2007. Sow Retention Needs Attention. http://enews.penton.com/enews/nationalhogfarmer/north_american_preview_0/2007_november_2_north_american/display Accessed Nov. 2, 2007.

Hasty, P., J. Campisi, J. Hoeijmakers, H. van Steeg, and J. Vijg. 2003. Aging and genome maintenance: Lessons from the mouse. Science 299:1355–1359.

Hekimi, S., and L. Guarente. 2003. Genetics and the specificity of the aging process. Science 299:1351–1354.

Holl, J. W., and O. W. Robison. 2003. Results from nine generations of selection for increased litter size in pigs. J. Anim. Sci. 81:624–629.

Knauer, M., L. A. Karriker, T. J. Baas, C. Johnson, and K. J. Stalder. 2007. Accuracy of sow culling classifications reported by lay personnel on commercial swine farms. J. Am. Vet. Med. Assoc. 231:433–436.

Longo, V., and C. Finch. 2003. Evolutionary medicine: From dwarf model systems to healthy centenarians. Science 299:1342–1345.

Moore, C. 2001. Segregated production: How far could we go? Page 203 in A. D. Leman Swine Conf., Univ. Minnesota.

Mote, B. E., J. W. Mabry, K. J. Stalder, and M. F. Rothschild. 2009. Evaluation of current reasons for removal of sows from commercial farms. Prof. Anim. Sci. 25:1–7.

Mote, B. E., T. Serenius, K. J. Stalder, and M. F. Rothschild. 2006. The Holy Grail for pigs: Candidate genes affecting sow productive life. Proc. 8th World Congr. Genet. Appl. Livest. Prod., 20–22, Belo Horizonte, Minas Gerais, Brazil.

Oh, Y., S. R. Nagalla, Y. Yamanaka, H. S. Kim, E. Wilson, and R. G. Rosenfeld. 1996. Synthesis and characterization of insulin-like growth factor-binding protein (IGFBP)-7. Recombinant human mac25 protein specificically binds IGF-I and -II. J. Biol. Chem. 271:30322–30325.

Pla, L. M., C. Pomar, and J. Pomar. 2003. A Markov decision sow model representing the productive lifespan of herd sows. Agric. Syst. 76:253–272.

Roehe, R., and B. W. Kennedy. 1995. Estimation of genetic parameters for litter size in Canadian Yorkshire and Landrace pigs with each parity of farrowing treated as a different trait. J. Anim. Sci. 73:2959–2970.

Serenius, T., and K. J. Stalder. 2004. Genetics of length of productive life and lifetime prolificacy in the Finnish Landrace and Large White pig populations. J. Anim. Sci. 82:3111–3117.

Simon, A. F., C. Shih, A. Mack, and S. Benzer. 2003. Steroid control of longevity in *Drosophila melanogaster*. Science 299:1407–1410.

Stalder, K. J., R. C. Lacy, T. L. Cross, and G. E. Conatser. 2003. Financial impact of average parity of culled females in a breed-to-wean swine operation using replacement gilt net present value analysis. J. Swine Health Prod. 11:69–74.

Stalder, K. J., R. C. Lacy, T. L. Cross, G. E. Conatser, and C. S. Darroch. 2000. Net present value analysis of sow longevity and the economic sensitivity of net present value to changes in production, market price, feed cost, and replacement gilt costs in a farrow-to-finish operation. Prof. Anim. Sci. 16:33–40.

Stalder, K. J., A. M. Saxton, G. E. Conatser, and T. V. Serenius. 2005. Effect of growth and compositional traits on first parity and lifetime reproductive performance in U.S. Landrace sows. Livest. Prod. Sci. 97:151–159.

Tatar, M., A. Bartke, and A. Antebi. 2003. The endocrine regulation of aging by insulin-like signals. Science 299:1346–1351.